

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**



⑫

EUROPEAN PATENT APPLICATION

⑳ Application number : **94308954.0**

⑤① Int. Cl.⁶ : **A61K 31/55, A61K 9/48,
A61K 47/14**

㉔ Date of filing : **02.12.94**

③① Priority : **11.12.93 GB 9325395**

④③ Date of publication of application :
14.06.95 Bulletin 95/24

⑧④ Designated Contracting States :
**AT BE CH DE DK ES FR GB GR IE IT LI LU NL
PT SE**

⑦① Applicant : **CIBA-GEIGY AG**
Klybeckstrasse 141
CH-4002 Basel (CH)

⑦② Inventor : **Henry, Roy Lindsay Allen**
26 Rushams Road
Horsham, W. Sussex, RH12 2NU (GB)
Inventor : **Matthews, Graham Paul**
101 Trafalgar Road
Horsham, W. Sussex, RH12 2QL (GB)

⑦④ Representative : **Sharman, Thomas et al**
CIBA-GEIGY PLC.
Patent Department,
Central Research,
Hulley Road
Macclesfield, Cheshire SK10 2NX (GB)

⑤④ **Pharmaceutical compositions containing staurosporine derivatives.**

⑤⑦ A pharmaceutical composition comprising a solution or dispersion of a staurosporine active ingredient in a saturated polyalkylene glycol glyceride such as a mixture of esters of C₈-C₁₈ saturated fatty acids with glycerol and polyethylene glycol. The composition may be administered in capsules or as a dispersion in an aqueous medium.

This invention relates to pharmaceutical compositions, particularly pharmaceutical compositions comprising a staurosporine as active ingredient.

US Patent 5 093 330 describes staurosporine and N-substituted derivatives thereof as pharmaceuticals for use in tumour inhibition and inflammation inhibition, for antibacterial use and for use in combating arterio-

5 sclerosis, diseases of the cardiovascular system and of the central nervous system. Many staurosporines have low solubility in water. For example, N-benzoylstaurosporine, an especially preferred compound, has a solubility of less than 0.1 mg/litre. The staurosporines have been found to have low or negligible bioavailability.

The formulation of an orally administrable preparation has proved problematic since formulation with materials which are conventionally used to improve bioavailability, including materials in which the staurosporines are soluble, has negligible or no effect on bioavailability.

It has now been found that by dispersing a staurosporine active ingredient in a saturated polyglycolised glyceride, i.e. a polyalkylene glycol-modified saturated fatty acid glyceride, bioavailability can be considerably increased and orally administrable formulations can be prepared.

15 Accordingly, the present invention provides a pharmaceutical composition comprising a solution or dispersion of a staurosporine active ingredient in a saturated polyalkylene glycol glyceride.

The staurosporine active ingredient may be any of those described in US Patent No. 5 093 330. Preferred compounds are N-acylstaurosporines including N-benzoylstaurosporine, N-(3-nitrobenzoyl)staurosporine, N-(3-fluorobenzoyl)staurosporine, N-trifluoroacetylstaurosporine, N-phenylcarbamoylstaurosporine, N-(3-carboxypropionyl)staurosporine, N-methylaminothiocarbonylstaurosporine, N-tert-butoxycarbonylstaurosporine, N-(4-carboxybenzoyl)staurosporine, N-(3,5-dinitrobenzoyl)staurosporine, N-(2-aminoacetyl)staurosporine, N-alanylstaurosporine and their pharmaceutically acceptable salts. An especially preferred active ingredient is N-benzoylstaurosporine.

The saturated polyalkylene glycol glyceride may be, for example, a mixture of glyceryl and polyethylene glycol esters of one or more long chain saturated fatty acids, usually C₈-C₁₈ saturated fatty acids. The acid component of such esters may be, for example, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid or a mixture of two or more thereof. The polyethylene glycol component of such esters generally has a molecular weight of 200 to 2000, preferably 1000 to 1800, especially 1400 to 1600. The glycerides, i.e. the glycol-modified glycerides, are usually mixtures of mono, di and triglycerides and polyethylene glycol mono and diesters.

Preferred polyalkylene glycol glycerides are those having a high Hydrophilic-Lipophilic Balance (HLB) value. Further preferred are glycerides which are mixtures of esters of one or more C₈-C₁₈ saturated fatty acids with glycerol and a polyethylene glycol having a molecular weight of 1000 to 2000, preferably 1200 to 1800, especially 1400 to 1600. An especially preferred material is available commercially from Gattefossé as Gelucire 44/14; this is a mixture of esters of C₈-C₁₈ saturated fatty acids with glycerol and a polyethylene glycol having a molecular weight of about 1500, the specifications for the composition of the fatty acid component being, by weight, 4-10% caprylic acid, 3-9% capric acid, 40-50% lauric acid, 14-24% myristic acid, 4-14% palmitic acid and 5-15% stearic acid.

The saturated polyalkylene glycol glycerides are either commercially available or may be prepared by known procedures. For example they may be obtained by partial alcoholysis of hydrogenated vegetable oils using the polyalkylene glycol, or by esterification of the saturated fatty acid, or mixture of such acids, using glycerol and the polyalkylene glycol.

In compositions of the invention, the staurosporine active ingredient is generally present in an amount from 1 to 30%, preferably 5 to 25%, especially 10 to 20%, by weight of the composition.

45 The compositions of the invention may also contain carriers or adjuncts such as those described in US Patent No. 5 093 330 or other conventional excipients. For oral administration, the composition may be contained in capsules, usually hard capsules of gelatin or soft capsules of gelatin mixed with a plasticiser such as glycerol or sorbitol, or may be used as a dispersion in an aqueous medium, such as water, saline solution or a mixture of water with another, water-miscible, pharmaceutically acceptable solvent, for example in an amount of 0.5 to 70, preferably 5 to 50% by weight, optionally together with a preservative, for example a conventional preservative such as a benzoate, particularly an ester of p-hydroxybenzoic acid such as the methyl, ethyl, n-propyl, n-butyl or benzyl ester thereof or the sodium salt of the ester and other excipients such as dispersing agents and suspending agents.

55 The present invention also provides a method of preparing a pharmaceutical composition as hereinbefore described which comprises melting a saturated polyalkylene glycol glyceride, mixing a staurosporine active ingredient with the molten glyceride and allowing the resulting mixture to solidify.

The glyceride is conveniently melted by heating to a temperature 10 to 20°C above its melting point before addition of the staurosporine active ingredient as a powder. Optional excipients may be added to the molten

mixture.

When a composition of the invention is to be administered in capsules, for example orally, the liquid mixture of the staurosporine active ingredient and glyceride may be poured into hard capsules or injected into soft capsules and allowed to solidify therein. Alternatively, the solid solution or solid dispersion obtained on cooling the liquid mixture of the staurosporine active ingredient and glyceride may be remelted for introduction into capsules. The capsules may contain, for example, from 1mg to 250mg of the staurosporine active ingredient.

When a composition of the invention is to be administered as a dispersion in an aqueous medium, e.g. water, a saline solution or mixture of water with a water-miscible pharmaceutically acceptable solvent, the solid solution or solid dispersion obtained on cooling the liquid mixture is conveniently broken up and dispersed in the aqueous medium by stirring or by ultrasonication.

The compositions of the invention may be used in the treatment of the indications hereinbefore described. The compositions may be administered in prophylactically or curatively effective amounts. For example, compositions containing daily doses of 1 to 1000mg of the active ingredient may be administered to warm-blooded animals having a body weight of about 70kg. The compositions are particularly useful in the treatment of cancer.

The invention is illustrated by the following Examples, in which parts are by weight.

Example 1

Gelucire 44/14 (82 parts) is melted by heating to 60°C. Powdered N-benzoylstaurosporine (18 parts) is added to the molten material. The resulting mixture is homogenised and the dispersion obtained is introduced into hard gelatin capsules of different size, so that some contain a 25mg dosage and others a 75mg dosage of the staurosporine. The resulting capsules are suitable for oral administration.

Example 2

Gelucire 44/14 (86 parts) is melted by heating to 60°C. Powdered N-benzoylstaurosporine (14 parts) is added to the molten material. The mixture is homogenised and the dispersion obtained is introduced into hard gelatin capsules of different size, so that some contain a 25mg dosage and others a 75mg dosage of the staurosporine. The resulting capsules are suitable for oral administration.

Example 3

The bioavailability of N-benzoylstaurosporine dispersed in Gelucire 44/14 is tested as follows:

Dosages of 100mg of N-benzoylstaurosporine dispersed in 500mg of Gelucire 44/14 are administered orally in size O gelatine capsules to two healthy random bred pedigree male beagle dogs weighing 10-15kg.

Blood samples (4ml) are collected from each dog prior to administration and at various time intervals after administration. Each sample is immediately centrifuged and the separated plasma is protected from light, frozen and stored in the dark at -20°C until analysed. The concentration of N-benzoylstaurosporine in each plasma sample is determined by high performance liquid chromatography using UV detection. The results are as follows:

Time (hours)	Concentration of N-benzoylstaurosporine in Plasma (μ mol/l)	
	Dog 1	Dog 2
0	0	0
1	0.27	0.23
2	0.38	0.30
3	0.36	0.45
4	0.31	0.41
6	0.27	0.40
8	0.24	0.28

Claims

1. A pharmaceutical composition comprising a solution or dispersion of a staurosporine active ingredient in a saturated polyalkylene glycol glyceride.
2. A composition according to claim 1, in which the staurosporine active ingredient is N-benzoylstaurosporine.
3. A composition according to claim 1 or 2, in which the glycol glyceride is a mixture of glyceryl and polyethylene glycol esters of one or more C₈-C₁₈ saturated fatty acids.
4. A composition according to claim 3, in which the glycol glyceride is a mixture of esters of one or more C₈-C₁₈ saturated fatty acids with glycerol and a polyethylene glycol having a molecular weight of 1000 to 2000.
5. A composition according to claim 4, in which the polyethylene glycol has a molecular weight of 1400 to 1600.
6. A composition according to any of the preceding claims, in which the staurosporine active ingredient is present in an amount of 1 to 30% by weight of the composition.
7. A composition according to claim 6, in which the staurosporine active ingredient is present in an amount of 10 to 20% by weight of the composition.
8. A composition according to any of the preceding claims contained in a capsule.
9. A composition according to any of claims 1 to 7 as a dispersion in an aqueous medium.
10. A composition according to claim 9, in which the dispersion contains 0.5 to 70% by weight of the composition.
11. A method of preparing a pharmaceutical composition which comprises melting a saturated polyalkylene glycol glyceride as specified in any of claims 3 to 5, mixing a staurosporine active ingredient as specified in claim 1 or 2 with the molten glyceride and allowing the resulting mixture to solidify.
12. A method according to claim 11, in which the staurosporine active ingredient is used in an amount specified in claim 6 or 7.



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 30 8954

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	CHEMICAL ABSTRACTS, vol. 112, no. 9, 26 February 1990, Columbus, Ohio, US; abstract no. 77240, * abstract * & WO-A-89 07105 (KYOWA HAKKO KOGYO CO., LTD., JAPAN) 10 August 1989 ---	1,2	A61K31/55 A61K9/48 A61K47/14
D,A	EP-A-0 296 110 (CIBA-GEIGY AG) * claims * * page 13, line 26 - line 65 * * page 14, line 1 - line 7 * ---	1-3	
A	CHEMICAL ABSTRACTS, vol. 112, no. 1, 1 January 1990, Columbus, Ohio, US; abstract no. 7781, * abstract * & JP-A-01 143 877 (ASAHI CHEMICAL INDUSTRY CO., LTD., JAPAN; KITASATO INSTITUTE) 6 June 1989 ---	1,2	
A	CHEMICAL ABSTRACTS, vol. 120, no. 21, 23 May 1994, Columbus, Ohio, US; abstract no. 270948, * abstract * & JP-A-05 247 055 (MEIJI SEIKA CO., JAPAN) 24 September 1993 ---	1,2	TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K
A	WO-A-93 07153 (SCHERING CORPORATION, U.S.A.) * claims * * page 10, line 4 - line 34 * * page 11, line 1 - line 34 * * page 12, line 1 - line 33 * * page 13, line 1 - line 5 * ---	1-3	
		-/--	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 24 March 1995	Examiner Scarponi, U
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure F : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons * : member of the same patent family, corresponding document</p>			

EPO FORM 150 (03.92) (P04031)



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 30 8954

DOCUMENTS CONSIDERED TO BE RELEVANT				
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claims	CLASSIFICATION OF THE APPLICATION (Int. CL.6)	
A	PATENT ABSTRACTS OF JAPAN vol. 010, no. 031 (C-327) 6 February 1986 & JP-A-60 185 719 (AJINOMOTO KK) 21 September 1985 * abstract *	1,2		
A	CHROMABSTRACTS, vol. 119, no. 5, 2 August 1993, Columbus, Ohio, US; abstract no. 40959, * abstract * & JP-A-05 097 708 (LION CORP., JAPAN) 20 April 1993	1-3		
A	WO-A-92 17181 (THE SECRETARY OF UNITED STATES DEPARTMENT OF COMMERCE) * claims * * page 12, line 25 - line 37 * * page 13, line 1 - line 38 * * page 14, line 1 - line 32 *	1-3		
A	EP-A-0 457 295 (THE ROCKEFELLER UNIVERSITY) * claims 1,6 * * column 8, line 20 - line 58 * * column 9, line 1 - line 35 *	1-3		TECHNICAL FIELDS SEARCHED (Int. CL.6)
A	DATABASE WPI Week 9008, Derwent Publications Ltd., London, GB; AN 90-055512 (08) * abstract * & JP-A-02 009 819 (ASAHI CHEM. IND. KK; KITASATO RES. INST.) 12 January 1990	1-3		
The present search report has been drawn up for all claims				
Place of search THE HAGUE		Date of completion of the search 24 March 1995	Examiner Scarponi, U	
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>				

EPO FORM 1503 (01/92) (P04021)